REMARKS

In the Specification

Applicants have amended the specification at page 1 to cross-reference the present application to earlier applications from which it claims priority.

Applicants have amended the specification to correct several inadvertent typographical errors. Specifically, applicants have corrected an inadvertent error at specification page 3, line 22; page 4, lines 2, 4 and 6; and page 6, lines 15, 20, 22 and 24. Applicants have corrected the valence of the carbon atom in the imine group ($N{=}C\underline{H}\text{-}N(R')_2$). Support for this amendment may be found in Table 1 of the specification at pages 20-21, compound nos. 48 and 50, and in Table 2, page 34, compound no. 140, which disclose specific inhibitors having imine moieties.

Applicants have corrected an inadvertent error at specification page 3, line 20, page 4, line 5 and page 6, lines 13 and 23. Applicants have corrected the valence of the nitrogen atom in the amide group ($CON\underline{H}R'$). Applicants have corrected an inadvertent error at specification page 4, line 5. Applicants have corrected the valence of the nitrogen atom in the secondary amine group ($N\underline{H}R^3$). These inadvertent errors would have been obvious to one having ordinary skill in the art because one would recognize that N is trivalent.

Applicants have also amended the specification to correct several obvious graphical errors in the chemical structures in the specification. Applicants inadvertently omitted hydrogen atoms in the heteroatom groups "-NH-" or "-OH-". Applicants have amended the compounds to correct these errors by replacing, "N" with "NH_2" or "NH", or "O" with "OH" as appropriate. See, page 10, the first two

compounds in row 4, the last compound in row 5, and all compounds in rows 6-7; page 11, the last compound in row 1, and all compounds in rows 2-3; page 41, Table 4, compound nos. 303-304; page 44, Table 4, compound no. 351; and pages 46-47, Table 4, compound nos. 358-360 and 372. These inadvertent errors would have been obvious to one having ordinary skill in the art because one would recognize that N is trivalent and O is bivalent.

Applicants have corrected an inadvertent typographical error in the specification on page 106, lines 2 and 4-8. Specifically, applicants have corrected the "less than" (<) and "greater than" (>) characters, which were inadvertently interchanged in the specification as originally filed. This inadvertent error would have been obvious to one having ordinary skill in the art because one would recognize that if "++" represents moderate LC_{50} or K_i values between "0.1 and 1.0 μM", then "+++" must represent more potent LC_{50} or K_i values, i.e., "less than 0.1 μM", as indicated by the character "<", and "+" must represent less potent LC_{50} or K_i values, i.e., "greater than 1.0 μM", as indicated by the character ">".

In the Claims

Applicants have amended claims 6, 11, 18, 21-24, 26-35 and 37-38. Claims 4-12, 15 and 18-38 are pending.

Applicants have amended claim 6 to correct inadvertent graphical errors. Applicants inadvertently omitted hydrogen atoms in the heteroatom groups "-NH-" and "-OH-". Applicants' amendment corrects this error by replacing, "N" with "NH_2" or "NH" and "O" with "OH" as appropriate.

Applicants have amended claim 11 to recite "-$N(R^2)$-, -$C(R^2)_2$-" within the definition of radical X. This amendment corrects the erroneous recitation of "-$N(R_2)$-, -$C(R_2)_2$-". Support for this amendment may be found in the specification as filed at page 7, line 16.

Applicants have amended claim 18 to improve its form.

Applicants have amended claims 21 and 38, to correct the valence of the carbon atom in the imine group (N=C<u>H</u>-N(R')$_2$). Applicants have corrected this error by replacing "-N=C-N(R')$_2$" with "–N=CH-N(R')$_2$". Support for this amendment may be found in Table 1 of the specification at pages 20-21, compound nos. 48 and 50, and in Table 2, page 34, compound no. 140, which disclose specific inhibitors having imine moieties. Further, one having ordinary skill in the art would recognize that carbon is tetravalent.

Applicants have amended claims 22-24 to represent the compounds recited in the claims. Support for this amendment may be found throughout the specification. See, e.g., page 35, lines 1-5 and Tables 3-5 on pages 40-51.

Applicants have amended claim 26 to recite that the method may be used to treat, *inter alia*, viral disease, myocardial ischemia and renal ischemia. Support for this amendment may be found throughout the specification. See, e.g., originally filed claims 32 and 34 and page 54, lines 18-21 and 27-30.

Applicants have amended claims 26-37 to delete reference to a method of preventing a disorder. Applicants make this amendment solely to expedite prosecution and reserve the right to pursue the cancelled subject matter in applications claiming benefit herefrom.

Applicants have further amended claim 26 to delete the term "allergies" because it is cited in claim 27.

Applicants have further amended claim 26 to correct the spelling of the enzyme prostaglandin endoperoxide synthase-2. This enzyme is variously known as endoperoxidase synthase-2 or endoperoxide synthase-2. However, applicants have amended claim 26 to recite "endoperoxide synthase-2". Support may be found throughout the specification. See, e.g., originally filed claim 35 and page 55, lines 1-2.

Applicants have amended claim 38 to define an aromatic heterocycle. Specifically, applicants' amended claim 38 defines that "the heterocyclic ring comprises 1-2 heteroatoms independently selected from N, O or S". Support for this amendment is found in the specification at page 9, line 1, which recites a pyridyl and compound nos. 123 and 372 (heteroatom is one or two nitrogen atoms) on pages 32 and 47; benzo[1,3]dioxol on page 10, line 5, compound nos. 355 and 357 (heteroatom is one or two oxygen atoms); and compound nos. 317-318, 326, 338-339, 347 and 356 (heteroatom is sulfur atom) on pages 42-44 and 46.

Applicants have further amended claim 38 to recite additional substituents within the definition of radical Q_2. Applicants have amended claim 38 such that radical Q_2 may be directly substituted with CH=N-OH or CH=O. Support for this amendment may be found at in Table 4, page 42, compound nos. 307 and 316. Further, applicants have amended claim 38 such that the Q_2 C_1-C_3 straight or branched alkyl optional substituent may be further optionally substituted with the following (support for the amendment follows the substituent): NH–CH_3 (Table 4, page 41, compound no. 303), $NHCH_2CH_2OH$ (Table 4, page 44, compound no. 351),

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$NHCH_2CH(OH)CH_2OH$ (Table 4, page 46, compound no. 360), $CH_2OCH_2OCH_2$ (Table, 4, page 49, compound No 393), $NHCH_2CH_2NH_2$ (Table 4, page 46, compound no. 359), NH-phenyl (Table 4, page 46, compound no. 358), piperazinyl (Table 4, page 41, compound no. 304) and pyrrolidinyl (Table 4, page 44, compound no. 350).

Applicants have also amended claim 38 to recite the substituent -CH(OH) within the definition of radical X. Support for this amendment may be found in Table 3, page 40, compound no. 208.

Applicants have amended claim 38 to clarify the subject matter by replacing "CONR'" with "CONHR'", thus correcting the valency of the amide. Furthermore applicants have corrected an inadvertent error by replacing "NR^3" with "NHR^3", thus clearly identifying the secondary amine functionality. These inadvertent errors would have been obvious to one having ordinary skill in the art because one would recognize that nitrogen is trivalent.

None of the above amendments adds any new subject matter. Their entry is requested.

THE REJECTIONS

I. 35 U.S.C. § 112, first paragraph

(1) The Examiner has rejected claims 38, 4-12, 15, 18-21 and 25-37 under 35 U.S.C. § 112, first paragraph, asserting that the disclosure does not reasonably provide enablement for embodiments of radicals other than phenyl and pyridyl for Q_1; phenyl, thienyl, benzofuran, benzothiophene and indolyl for Q_2; and phenyl for Q_3. Specifically, the Examiner asserts that the specification does not

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provide a sufficient enabling disclosure for making the diverse scope of radicals Q_1, Q_2, and Q_3. The Examiner contends that the specification does not provide adequate representation of examples or reasonable disclosure of starting material sources to be the applicants' invention. Applicants traverse.

First, applicants have enclosed herewith additional compounds that are encompassed by the claims. See, e.g., Exhibit A, Tables 1-3 for 77 additional compounds. All of these 77 compounds fall within the scope of the claimed subgenera (If), (Ig) and (Ih) and were synthesized according to the teachings of the specification. See the Declaration under 37 C.F.R. § 1.132 by Francesco Gerald Salituro (hereafter "the Salituro declaration"), ¶ 6 and Exhibit A, Tables 1-3. Further, all of the compounds exhibit p38 inhibitory activity. See the Salituro declaration, ¶¶ 7-8 and Tables 1-3 of Exhibit A. Thus, applicants have exemplified compounds comprising radical Q_1 with substituted phenyl rings (see, e.g., pages 9-11 and Table 5, pages 50-51, of the specification and compounds 701-712 and 714-737 of Table 2 of Exhibit A) and benzo[1,3]dioxole (see, e.g., compound no. 713, Table 3 of Exhibit A), and have demonstrated the efficacy of these compounds. Applicants have also disclosed substituted pyridyl rings as a preferred embodiment of radical Q_1 (see, page 8, lines 15-16 and page 10, row 5).

Second, the originally-filed specification teaches how to attach any of the claimed Q_1 ring systems to the heterocyclic core of formulae (If) and (Ih) by reacting a dibromopyridine derivative with a Q_1-amine. See, e.g., schemes 7 and 8, step 1, pages 37-38. As explained in the Salituro declaration, one having ordinary skill in the art would know how to synthesize the full scope of the claimed compounds of

formulae (If) and (Ih) by using other amine-substituted Q_1 ring systems. See the Salituro declaration, ¶ 10. These amine-substituted rings systems are available commercially or are readily synthesized by one having ordinary skill in the art. See the Salituro declaration, ¶ 10. Therefore, one of ordinary skill in the art following the teachings of the specification would know how to synthesize analogous compounds having any one of the Q_1 ring systems that fall within the claimed scope of compounds of formulae (If) and (Ih). See the Salituro declaration, ¶ 10.

Applicants have also exemplified compounds comprising radical Q_2 with a variety of substituted or unsubstituted aromatic carbocycles or heterocycles. The originally-filed specification teaches several synthetic routes for attaching the Q_2 ring system, along with the spacer group X if present, to the heterocyclic core of formulae (Ie), (Ig), (If) and (Ih). See, e.g., scheme 3, step 2, pages 26-27, and schemes 7 and 8, step 2, pages 37-38. Specifically, scheme 3 teaches a synthetic route using an aryl lithium compound, while schemes 7 and 8 teach two different synthetic routes using arylstannane derivatives (Q_2-$Sn(R)_3$ or phenylboronic acid derivatives (Q_2-boronic acid), respectively. There are many aryl-lithium-substituted, arylstannyl-substituted and arylboronic acid-substituted derivatives that are commercially available and/or easily synthesized. See the Salituro declaration, ¶ 11. One having ordinary skill in the art would be able to use these derivatives as starting materials to produce the compounds of this invention. See the Salituro declaration, ¶ 11. Therefore, given the synthetic schemes known in the art or provided in the specification and the readily available starting materials, one having ordinary skill in the art would know how to synthesize compounds having any one of the Q_2 ring systems that fall within the

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claimed scope of compounds of formulae (Ie), (Ig), (If) and (Ih). See the Salituro declaration ¶ 11.

Applicants have exemplified radical Q_3 with substituted phenyl rings. See, Tables 3 and 4, pages 40-50. In addition, applicants have exemplified compounds of formulae (Ig) wherein radical Q_3 is a substituted benzo[1,3]dioxole ring (see, e.g., compound nos. 501-502 and 505-506, Table 1, Exhibit A) and a substituted pyridyl ring (see, e.g., compound nos. 519-521, 528-534 and 544, Table 1, Exhibit A). The specification as originally-filed teaches how to attach the Q_3 ring system to the heterocyclic core of formulae (Ie) and (Ig). See, e.g., schemes 1-4, step 1, pages 24-27 and page 37, lines 2-4. Specifically, reaction schemes 1-4 teach how to attach a nitrile-substituted aromatic carbocyclic or heterocyclic derivative (Q_3-CN) to the heterocyclic core of formulae (Ie) and (Ig). There are many nitrile-substituted aromatic carbocycles or heterocycles commercially available and/or easily synthesized and any of these nitrile-substituted heterocycles may be used as starting materials to produce the compounds of this invention. See the Salituro declaration, ¶ 12. Therefore, one having ordinary skill in the art would know how to synthesize compounds that fall within the claimed scope of compounds of formulae (Ie) and (Ig) by following the teachings of the specification. See the Salituro declaration, ¶ 12.

Applicants have also provided a detailed descriptions for synthesizing compounds in the Examples. See, e.g., compound nos. pre-1, pre-2, pre-5 and pre-6 on pages 64-70, and compound no. 201, on page 75, compound no. 202 on page 80, and compound no. 410 on page 83. Thus, the embodiments exemplified in the present invention coupled with the synthetic schemes provided by applicant and the availability

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of starting materials would readily enable one of skill in the art to practice the invention as claimed.

Accordingly, applicants submit that the specification as filed teaches how to make the full scope of radicals Q_1, Q_2 and Q_3 as recited by the pending claims. See, e.g., the Salituro declaration, ¶ 13.

(2) The Examiner has rejected claims 38, 4-12, 15, 18-21 and 25-37 under 35 U.S.C. § 112, first paragraph, asserting that there is no reasonable basis for assuming that the range of compounds claimed will all share the same physiological properties. Applicants traverse.

Applicants have exemplified 107 compounds in the specification with a diverse range of Q_1, Q_2 and Q_3 radicals that fall within the scope of the claimed invention. Applicants have also disclosed the ability of these 107 specific compounds to inhibit phosphorylation of the EGF receptor peptide, a phosphoryl acceptor, in a p38-catalyzed kinase reaction. See, e.g., Table 7, pages 101-106. Applicants have also provided the results of other p38 inhibition assays for some of these compounds. See *Id.*

Applicants have enclosed herewith additional data for 77 compounds, including their inhibitory constants (Ki) and IC_{50} values. See, e.g., Tables 1-3, Exhibit A and the Salituro declaration, ¶¶ 7-8. Each of these 77 compounds falls within the scope of the claimed subgenera (If), (Ig) and (Ih) and all of them show p38 inhibitory activity. See, Tables 1-3 *Id.* and the Salituro declaration, ¶¶ 7-8. Thus, applicants have provided close to 200 compounds that fall within the claimed scope of the invention that have p38 inhibitory activity.

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Further, contrary to the Examiner's contention, there is a reasonable basis for assuming that the claimed compounds will share similar physiological properties. The Declaration under 37 C.F.R. § 1.132 by Guy W. Bemis (hereafter "the Bemis declaration"), ¶¶ 4-6 and 8, discloses that the applicants have analyzed X-ray crystal structure results for the p38 kinase alone and complexed with a p38 inhibitor, and combined these results with computer modeling data. Applicants have used the combination of the X-ray crystal structure and computer modeling results to design compounds that are likely to have favorable interactions with the target p38 kinase protein. See, the Bemis declaration, ¶ 5. As discussed in greater detail in the Bemis declaration and below, the favorable interactions between a compound and the p38 kinase predict that the compound would have p38 kinase inhibitory activity. Thus, one of ordinary skill in the art would reasonably expect that the claimed compounds would have p38 inhibitory properties.

X-ray crystal structure data have shown that the Q_2 ring in formulae (Ie), (If), (Ig) and (Ih) occupies a pocket of the p38 kinase that includes amino acids Leu-104, Leu-75, Leu-86, Thr-106, Ile-84, and Lys-53. See the Bemis declaration, ¶ 8. Molecular modeling data have shown that the aromatic ring system of Q_2 in compounds of formulae (Ie), (If), (Ig) and (Ih) provides attractive interactions with the above- identified amino acids of p38 kinase. See *Id.* Further, the computer modeling data correlate well with the experimental results obtained for p38 inhibition with synthesized compounds. See, e.g., Table 7, pages 101-106 of the specification, Table 1 of Exhibit B and the Bemis declaration, ¶ 8. Therefore, one having ordinary skill in the art would reasonably expect that the compounds of formulae (Ie), (If), (Ig) and

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(Ih) having any of the Q_2 rings encompassed by the scope of amended claim 38 would have p38 inhibitory activity. See the Bemis declaration ¶ 8.

Applicants have also produced computer modeling data of representative compounds that fall within the genus of formula (Ih) wherein Q_1 is a diverse range of aromatic carbocyclic or heterocyclic rings. See Table 3, Exhibit B, compound nos. 31-36, and the Bemis declaration, ¶ 9. The Q_1 rings ranges from chloro-benzo[1,3]-dioxole (see, e.g., compound no. 31), naphthalene (see, e.g., compound nos. 32 and 33), chloro-pyrrole (see, e.g., compound no. 34), chlorobenzofuran (see, e.g. compound no. 35) and methyl-indole (see, e.g. compound no. 36).

Applicants have demonstrated that compound no. 31 is a potent inhibitor of p38. See, e.g., Table 3, Exhibit B. Applicants' computer modeling data show that compound nos. 32-36 would also bind to the p38 kinase and would have inhibitory activity in part because they share similar characteristics with compound no. 31. See the Bemis declaration, ¶¶ 9-10. Specifically, the modeling data show that the Q_1 rings of model compounds nos. 32-36 have the following characteristics that they share with compound no. 31: a) they have little internal strain energy, b) no steric clashes with amino acids at the site in p38 kinase where the Q_1 ring binds, and c) substantial hydrophobic contact with the hydrophobic surfaces of the p38 kinase, wherein the hydrophobic surfaces include those created by Tyr-35, Gly-110, Ala-111 and Asp-112. See the Bemis declaration, ¶ 10. Support for this prediction for the Q_1 ring is further provided by the results obtained for ring Q_2, wherein modeling data correlated well with the p38 inhibitory activity data. See the Bemis declaration, ¶ 10.

Although the computer modeling was performed with compounds of formula (Ih), one having ordinary skill in the art would recognize that compounds of formula (If) would exhibit similar attractive interactions between their Q_1 rings and p38 kinase. See the Bemis declaration, ¶ 11. Therefore, one having ordinary skill in the art would reasonably believe that the Q_1 rings encompassed by the claimed compounds of formulae (If) and (Ih) would interact similarly with p38 kinase such that the claimed compounds would have inhibitory activity. See the Bemis declaration, ¶ 11.

With respect to radical Q_3, ring Q_3 of compounds of formula (Ig) occupies the same pocket of p38 kinase as ring Q_1 of compounds of formula (Ih). See the Bemis declaration, ¶ 10. In addition, rings Q_1 and Q_3 are chemically and structurally similar to one another. See *Id.* and the pending claims. Thus, one having ordinary skill in the art would reasonably expect that compounds of formula (Ig) would be p38 inhibitors based upon the molecular modeling performed for compounds of formula (Ih). See the Bemis declaration, ¶ 10. In addition, one having ordinary skill in the art would reasonably expect that compounds of formula (Ie) would exhibit attractive interactions between their Q_3 rings and p38 kinase that would be similar to the interactions between the Q_3 rings of compounds of formula (Ig) and p38 kinase. See the Bemis declaration, ¶ 11. Thus, one of ordinary skill in the art would expect that compounds of formula (Ie) and (Ig) having any of the Q_3 rings encompassed by the scope of the claims would have p38 inhibitory activity.

Based on the demonstrated inhibitory ability of the 107 compounds disclosed in Table 7, the 77 compounds disclosed in Tables 1-3 in Exhibit A and the computer modeling data presented herein, one of skill in the art would expect that all

of the compounds within the scope of the claims would possess p38 inhibitory activity. See, e.g., the Bemis declaration, ¶ 12.

(3) The Examiner has rejected claims 26-37 under 35 U.S.C. § 112, first paragraph, asserting that the scope of the method claims is not adequately enabled based on the p38 inhibitory activity provided in the specification. The Examiner asserts that "it is inconceivable as to how the claimed compounds can not only treat but also 'prevent' a myriad of diseases with different etiologies". See p. 5 of the September 11, 2000 Office Action. Applicants traverse.

Merely to expedite prosecution, applicants have amended claims 26-35 and 37 to delete therefrom the term "preventing" or "prevent", thus obviating the Examiner's rejection.

Accordingly, applicants request that the Examiner withdraw this § 112, first paragraph rejection for the reasons provided above.

II. 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 38, 4-12, 15, and 18-37 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specific rejections are addressed individually below.

The Examiner has rejected claim 38 with respect to the structural representation of formulae (Ie), (If), (Ig) and (Ih). Specifically, the Examiner asserts that the structural representation has nodes that overlap with bonds and therefore, are

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not clearly comprehensible. The Examiner has also stated that formulae (Ie)-(If) and (Ig)-(Ih) have been interchanged in claim 28. Applicants traverse.

Applicants have obviated the Examiner's objection by amending claim 38 1) to represent clearly the structures referred to by the Examiner; and 2) to correct the structures of formulae (Ie), (If), (Ig) and (Ih) to refer to the accurate structure, as shown in the specification at page 35, lines 3-5.

The Examiner has further rejected claim 38 with respect to the definition of the "heterocyclic ring systems" for radicals Q_1, Q_2 and Q_3. Specifically, the Examiner asserts that definition does not set forth the type and number of heteroatoms in each heterocyclic ring. Applicants traverse in light of the amendments to claim 38.

Applicants have obviated the Examiner's objection by amending claim 38 to specify the type and number of heteroatoms that may be included in a heterocyclic ring of radicals Q_1, Q_2 and Q_3.

The Examiner states that there is a period (.) in the body of claim 38. Applicants traverse in light of the amendments to claim 38.

Applicants have deleted the period and replaced it with a semi-colon. Thus, applicants have obviated the Examiner's objection by amending claim 38 to correct this error.

The Examiner states that a definition is provided for R_1 but that this variable is absent in the structural formulae or in the definition of other variables. Applicants traverse in light of the amendments to claim 38.

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Applicants have obviated the Examiner's objection by amending claim 38 to delete the term "R_1".

The Examiner states that a number of structures on pages 115-116 have open valencies. Applicants traverse.

Applicants have obviated the Examiner's objection by amending claim 6. Applicants had inadvertently omitted hydrogen atoms in the heteroatom group "-NH-" and substituent "OH" and "NH_2". Applicants have amended these inadvertent graphical errors by replacing, "N" with "NH_2" or "NH" or "O" with "OH" as appropriate.

The Examiner has rejected claim 7, asserting that there is insufficient antecedent basis for the limitation "2-chloro-4-hydroxyphenyl, 2-chloro-4-aminophenyl" in claim 6.

Applicants have obviated the Examiner's objection by amending claim 6 to correct the structures, as noted above. Thus, as amended, claim 6 has the requisite antecedent basis for the limitation in claim 7.

The Examiner has rejected claim 11, asserting that there is insufficient antecedent basis for the limitation "-NR-, -$C(R_2)$-" in claim 38 on which claim 11 is dependent. Specifically, the Examiner states that claim 38 recited "-$N(R^2)$-, -$C(R^2)_2$-" as a definition of radical X. Applicants traverse.

Applicants have amended claim 11 to recite "-$N(R^2)$-, -$C(R^2)_2$-". As amended, claim 11 has the requisite antecedent basis for this limitation.

The Examiner has rejected to claim 18, lines 4-5, asserting that the phrase "to the rest of the inhibitor" is confusing. Applicants traverse.

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Applicants have obviated the Examiner's objection and replaced the phrase "rest of the inhibitor" with "compound". As amended, claim 18 refers clearly to the compound to which it is drawn.

The Examiner has rejected claim 22, asserting that "the claim does not show the species claimed and refers to the specification." Additionally, the Examiner states that "the formula (Ie) is different from that of the specification." Applicants traverse.

Applicants have obviated the Examiner's objection by depicting the chemical structures of formula (Ie) and the compounds recited in the claims. Applicants have also corrected structure (Ie) in claim 38 as described above.

The Examiner has rejected claim 23, asserting that "the claim does not show the species claimed and refers to the specification." Additionally, the Examiner states that "the formula (Ig) in claim 38 is different from that of the specification." Applicants traverse.

Applicants have obviated the Examiner's objection by depicting the chemical structures of formula (Ig) and the compounds recited in claim 23. Applicants have also corrected structure (Ig) in claim 38, as described above.

The Examiner has rejected claim 24, asserting that "the claim does not show the species claimed and refers to the specification." Additionally, the Examiner states that "the formula (Ih) in claim 38 is different from that of the specification." Applicants traverse.

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Applicants have obviated the Examiner's objection by depicting the chemical structures of formula (Ih) and the compounds recited in claim 24. Applicants have also corrected structure (Ih) in claim 38, as described above.

The Examiner has rejected to claim 27, asserting that the recitation of allergies as a subset of inflammatory disorders is confusing and unclear because claim 26, which provides antecedent basis for claim 27, lists "inflammatory diseases" and "allergies". Applicants traverse.

Applicants have obviated the Examiner's objection by deleting "allergies" from the list of disorders in claim 26.

The Examiner has rejected claim 32, asserting that there is insufficient antecedent basis for "a viral disease" in claim 26, on which claim 32 is dependent.

Applicants have amended claim 26 to add "viral diseases", thus obviating this rejection.

The Examiner has rejected claim 34, asserting that there is insufficient antecedent basis for the limitation "myocardial ischemia, renal ischemia" in claim 26, which provides antecedent basis for claim 34.

Applicants have amended claim 26 to recite "myocardial ischemia" and "renal ischemia", thus obviating this rejection.

The Examiner has objected to claim 35, asserting that there is insufficient antecedent basis for the term "endoperoxide", in line 3. Specifically, the Examiner asserts that claim 26, which provides antecedent basis for claim 35, recites "endoperoxidase". Applicants traverse.

Applicants have obviated the Examiner's objection by amending claim 26 to recite "endoperoxide".

In light of the above amendments, applicants request that the Examiner withdraw these § 112, second paragraph rejections.

CONCLUSION

Applicants request that the amendments presented herewith be entered, the accompanying arguments be considered and the claims be allowed to pass to issue.

Respectfully submitted,

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